Genetic and clinical features of patients with cystic fibrosis diagnosed after the age of 16 years

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Abstract

Background **– Cystic fibrosis is usually diagnosed in childhood, but a number of patients are not diagnosed until adulthood. The aim of this study was to investigate whether patients diagnosed at an older age had a different genetic constitution, manifestations of disease, and prognosis from those diagnosed at an early age.**

Methods **– Clinical data and results of lung function tests and DNA analysis of 143 adult patients with cystic fibrosis were entered into a computerised database. Patients diagnosed before their 16th birthday (early diagnosis, ED) were compared with those diagnosed at 16 years of age or older (late diagnosis, LD).**

Results **– Mean age of diagnosis of the ED group was 4·6 years compared with 27·7 years for the LD group. Mean (SD) percentage predicted pulmonary function was better for the LD group than for the ED group: forced expiratory volume in one second (FEV_1) 72·5 (31·1)% and 52·0 (24·8)%, and forced vital capacity (FVC) 89·8 (25·7)% and 71·9 (23·0)%, respectively. Colonisation with *Pseudomonas aeruginosa* was present in 70% of the ED group and 24% of the LD group. In the ED group 81% had pancreatic insufficiency compared with only 12% of the LD group. None of the LD group was homozygous for ΔF508 compared with 58% of the ED group. In the LD group 72% were compound ΔF508 heterozygotes and 28% had two non-ΔF508 mutations.**

Conclusions **– Among this group of 143 adult patients with cystic fibrosis late diagnosis is caused mainly by delayed expression and mild progression of clinical symptoms. Late diagnosis is associated with milder pulmonary disease, less pancreatic insufficiency, and different cystic fibrosis mutations. Since mortality in cystic fibrosis depends on the progression of pulmonary disease, patients with a late diagnosis have a better prognosis than those diagnosed early.**

(*Thorax* 1995;**50**:1301–1304)

Keywords: cystic fibrosis, late diagnosis, prognosis.

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Received 17 February 1995
Returned to authors
28 April 1995
Revised version received
27 June 1995
Accepted for publication
22 August 1995

Cystic fibrosis is the most common serious genetic disorder among Caucasian populations with an incidence of about one in 2500 live births and with one in 25 persons as asymptomatic carriers.[1] The disease is caused by mutations in the gene coding for the cystic fibrosis transmembrane conductance regulator (CFTR), a c-AMP dependent chloride channel.[2–4]

Most patients with cystic fibrosis in northern Europe have a mutation that causes the deletion of amino acid 508 (phenylalanine) of the CFTR protein, the so-called ΔF508 mutation.[5] In The Netherlands the frequency of this mutation on chromosomes of patients with cystic fibrosis is 77·1%.[6] More than 400 other mutations of the CFTR gene have now been found and most of them are rare.[6 7]

Cystic fibrosis is usually diagnosed in childhood, with up to 50% of patients presenting in the first year of life.[8] Typical modes of presentation are meconium ileus, failure to thrive, recurrent pulmonary infections, diarrhoea, and steatorrhea. It may, however, be diagnosed in adult patients.[8–11] Patients diagnosed late usually present with respiratory symptoms, or with male infertility due to congenital bilateral absence of the vas deferens (CBAVD).[12]

Diagnosis is confirmed by pilocarpine sweat iontophoresis, with chloride levels in sweat exceeding 70 mmol/l. Diagnosis can also be made with electrophysiological tests of nasal[13] or rectal epithelium.[14]

In our centre for adult patients with cystic fibrosis we define late diagnosis (LD) as diagnosis at the age of 16 or older. Patients diagnosed before their 16th birthday are considered to have an early diagnosis (ED). Almost 20% of our patients with cystic fibrosis were diagnosed after their 16th birthday. In this study we compared the characteristics of this group of LD patients with the characteristics of ED patients.

Methods

One hundred and forty three adult patients with cystic fibrosis who attended our clinic and for whom complete data (including DNA analysis) was available on 1 January 1995 were studied. Diagnosis was made by characteristic symptoms of cystic fibrosis, together with a chloride concentration in sweat of >70 mmol/l. Sweat tests were usually performed at the referring hospital by various methods (classic pilocarpine test, chloride electrode, etc), and are not directly comparable. In a small number of patients the sweat test results were equivocal so electrophysiological tests of rectal epithelium

were performed to confirm the diagnosis of cystic fibrosis.[14]

One hundred and thirty eight patients were Dutch, two were of Italian–Dutch descent, two were of Indonesian descent and one was of Chinese descent. There were 13 sets of siblings in our sample: a family of four, a family of three, and 11 sibling pairs, among them one pair of twins.

Demographic data including age, sex, age at diagnosis, presenting signs, and smoking history were taken from patients' charts. Age at diagnosis was determined as the age on the day of a first positive sweat test. For height and weight the values measured at the last clinic visit were used. Body mass index was calculated as weight/height^2 (weight in kilograms, height in metres). The presenting signs were those that caused the patient to seek medical attention and were categorised as follows: gastrointestinal complaints including diarrhoea, steatorrhoea, vomiting and abdominal pain; meconium ileus and rectal prolapse; ear, nose and throat complaints including nasal polyps and recurrent or chronic sinusitis.

Lung function tests were regularly performed in all patients and the best values for forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) over the previous year was used. The values were compared with reference values of the European Respiratory Society.[15] An age-independent yearly decline in FEV_1 was calculated by dividing the difference between predicted FEV_1 and actual FEV_1 (expressed as a percentage of reference values) by age.

Patients with consecutive sputum cultures growing *Pseudomonas aeruginosa* for at least six months were considered to be colonised with this microorganism.

Pancreatic insufficiency was considered to be present when patients had a faecal fat excretion of >10% fat intake during three day fat balance studies, or when gross steatorrhoea necessitated the use of pancreatic enzyme supplements, and diabetes mellitus (DM) was considered to be present when insulin was needed to control a patient's blood glucose concentration.

DNA was analysed for the following mutations: E60X, R117H, A455E, ΔI507, ΔF508, G542X, S549N, G550X, G551D, R553X, R560T, R1162X, S1251N, W1282X, N1303K, 621+1G→T, 1717-1G→A. These mutations represent 80% of the expected cystic fibrosis mutations in The Netherlands. DNA testing was done at the University of Groningen, Department of Medical Genetics and at University Hospital Rotterdam, Department of Clinical Genetics.

All data were entered into a computerised database. Continuous variables were compared by a two tailed unpaired t test. Categorical variables were compared using the χ^2 test. A p value of <0·05 was considered significant.

Results

Table 1 summarises the demographic data of the patient population. There were 118 patients with ED and 25 with LD. The mean age of the ED and LD patients was 26·8 and 35·7 years, respectively. The mean age of diagnosis in the ED group was 4·6 years (31 patients were diagnosed in the first year of life), and 27·7 years in the LD group. The mean height was below average for both men and women in the ED group: average height for men was around the 15th percentile and for women the 30th percentile for height compared with the normal Dutch population.[16] In the LD group both men and women were around the 50th percentile for height. Body mass index (BMI) was a little higher in the LD group (p=0·05), although for both groups it fell in the normal range (20·2 (2·4) in the ED group and 21·4 (2·8) in the LD group).

In the ED group 47% presented with recurrent respiratory tract infections, 45% with abnormal stools and other gastrointestinal tract symptoms, 5% with meconium ileus, 2·5% with rectal prolapse, 14% with poor growth or weight gain, and 6% with ENT symptoms such as nasal polyps or recurrent sinusitis. In 14% diagnosis was made because of a sibling or family member with cystic fibrosis (because many patients had more than one presenting symptom, the total exceeds 100%). In the LD group the presenting signs were recurrent respiratory tract infections in 92%, gastrointestinal tract complaints in 8%, one patient (4%) presented with male infertility, and one patient (4%) with oesophageal varices. In 24% the diagnosis was made because of cystic fibrosis in a sibling.

DNA of all patients was analysed for CFTR mutations. In the ED group the ΔF508 mutation was found on 74·2% of all cystic fibrosis chromosomes tested. Sixty eight patients (47%) were homozygous for the ΔF508 mutation (table 2). In the LD group the frequency of the ΔF508 mutation was 36·0%, and none of the patients was homozygous for this mutation (table 2). The difference between the two groups is highly significant (p<0·0001).

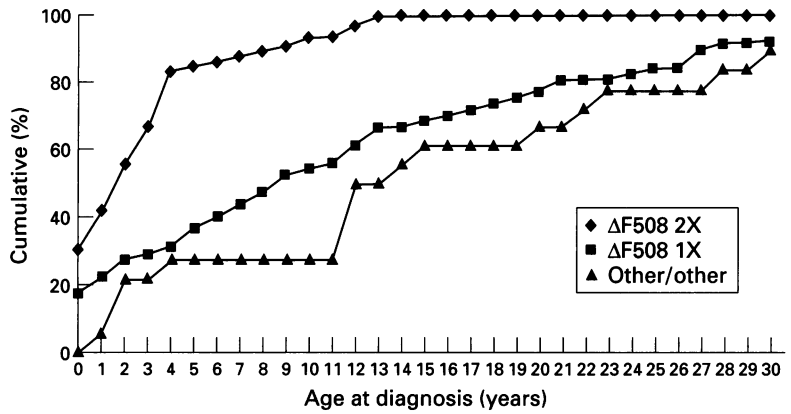
Table 1 Basic characteristics of early and late diagnosis groups

	Early diagnosis (n=118)	*Late diagnosis (n=25)*	*p*
Men/women (abs. number (%))	62/56 (53/47)	12/13 (48/52)	NS
Mean age (range) (years)	26·8 (15·8–42·7)	35·7 (21·4–55·6)	<0·005
Mean age at diagnosis (range) (years)	4·6 (0·0–15·9)	27·7 (16·9–43·4)	<0·005
Mean height (height percentile) men	1·75 (12·9)	1·83 (53·9)	<0·05
Mean height (height percentile) women	1·66 (33·0)	1·68 (44·0)	NS
BMI	20·2 (2·4)	21·4 (2·8)	<0·05

BMI = body mass index.

Table 2 Presence of ΔF508 mutation in 136 patients

	All patients	*Early diagnosis*	*Late diagnosis*
ΔF508 2X	68 (47%)	68 (58%)	0 (0%)
ΔF508 1X	57 (40%)	39 (33%)	18 (72%)
Two other mutations	18 (13%)	11 (9%)	7 (28%)
ΔF508 frequency	67·3%	74·2%	36·0%



Cumulative percentages of patients with cystic fibrosis diagnosed by age and by the presence of ΔF508 mutation.

Table 3 CFTR mutations in 278 chromosomes of adult cystic fibrosis patients

	Early diagnosis (n=118)		*Late diagnosis (n=25)*	
	n	*%*	*n*	*%*
ΔF508[s]	175	74·2	18	36·0
A455E[m]	12	5·1	14	28·0
1717-1[s]	6	2·5	1	2·0
G542X[s]	4	1·7	—	
W1282X[s]	3	1·3	—	
R553X[s]	1	0·4	1	2·0
S1251N	2	0·8	—	
N1303K[s]	1	0·4	—	
E60X	1	0·4	3	6·0
Not identified	31	13·2	13	26·0
Total	236		50	

Mutations not found: R117H, ΔI507, S549N, G550X, G551D, R560T, R1162X, 621+1G→T.
Mutations marked 's' are considered severe, those marked 'm' are considered mild.[29]

The influence of the presence of the ΔF508 mutation on the age of diagnosis is shown in the figure. All ΔF508 homozygotes were diagnosed by age 13, whereas 39% of patients not bearing the ΔF508 mutation were diagnosed at an age older than 16 years. The frequency of all CFTR mutations found is listed in table 3. The A455E mutation was relatively frequent in the LD group. In the ED group 13·2% of mutations could not be identified compared with 26·0% in the LD group.

Table 4 Mean (SD) pulmonary parameters expressed as a percentage of predicted values

	Early diagnosis (n=118)	*Late diagnosis (n=25)*	*p*
FEV_1	52·0 (24·8)	72·5 (31·1)	<0·005
FVC	71·9 (23·0)	89·8 (25·7)	<0·005
Yearly decline in FEV_1	1·82 (0·97)	0·74 (0·88)	<0·005
No. (%) colonised with *P aeruginosa*	83 (70·3%)	6 (24%)	<0·005

FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity.

Table 5 Number of patients (%) with non-pulmonary disease symptoms

	Early diagnosis (n=118)	*Late diagnosis (n=25)*	*p*
Pancreatic insufficiency	96 (81%)	3 (12%)	<0·005
Diabetes mellitus	17 (14%)	2 (8%)	NS

Table 4 lists the results of lung function tests for the two groups. In the ED group FEV_1 and FVC were significantly lower than in the LD group, despite the average higher age of the latter group. In both groups of patients the decline in FEV_1 was faster than in the general population. However, the average annual decline in FEV_1 was more than twice as large in ED patients than in LD patients. In the ED group a decline of FEV_1 to 30% is predicted by 38·3 years and for the LD group at 94·9 years. When the FEV_1 falls below 30% the likelihood of death within two years is increased and serious disability can be anticipated.[17]

In the ED group colonisation with *Pseudomonas aeruginosa* was present in 83 patients (70·3%) compared with six patients (24%) in the LD group (p<0·005).

There was one active smoker in the ED group, and one active and seven former smokers in the LD group.

Non-pulmonary disease symptoms are summarised in table 5. Pancreatic insufficiency was present in 96 patients (81%) of the ED group compared with only three (12%) in the LD group (p<0·005). Diabetes mellitus occurred in 17 patients (14%) in the ED group and in two (8%) of the LD group (NS). All ED patients with diabetes had an exocrine pancreatic insufficiency. In the LD group one of the patients with diabetes had an exocrine pancreatic insufficiency while in the other patient diabetes was associated with the use of oral corticosteroids.

Discussion

This study describes the clinical and genetic features of patients in whom cystic fibrosis was diagnosed late compared with those in whom it was diagnosed early. Late diagnosis appears to be not just a case of doctor or patient delay, but to constitute a separate patient group with a distinct genetic constitution and often milder pulmonary and non-pulmonary disease symptoms.

In earlier descriptions of groups of adult patients with cystic fibrosis 3·5–21% were diagnosed at 16 years or older.[8 18–22] In these reports on adult patients late diagnosis was not associated with milder disease. In fact, it was found that patients diagnosed at an early age generally did better than those diagnosed at a later age[23 24] or there was no difference.[19 22] However, our study shows that late diagnosis does not necessarily have to be detrimental to prognosis.

There are a number of reasons for late diagnosis. Firstly, mild or absent symptoms may delay a patient seeking medical attention. Secondly, a physician may not recognise cystic fibrosis, especially when the presenting symptoms are atypical. Finally, there may be problems in the diagnosis of cystic fibrosis as, for example, when there are repeated normal or borderline sweat tests.[25 26]

Most of those diagnosed early presented with a combination of gastrointestinal and pul-

monary symptoms, while in the late diagnosis group most were diagnosed because of recurrent pulmonary infections or because cystic fibrosis was found in a sibling. Gastrointestinal symptoms rarely led to the diagnosis of cystic fibrosis in this group. Until now the cystic fibrosis genotype was not predictive for pulmonary function or for prognosis.[27] Our results make it much more likely that there is a link between CFTR mutations and the severity of pulmonary disease. Among our patients all ΔF508 homozygotes were in the early diagnosis group who had more severe pulmonary and non-pulmonary disease. Most of those diagnosed at 16 years or older were pancreatic sufficient, which is closely related to the type of CFTR mutation.[28 29] The A455E mutation was frequently found among this group of patients and preliminary studies indicate that this mutation, known to be related to pancreatic sufficiency,[29] may be associated with mild pulmonary disease.[30] It seems that other CFTR mutations (some of which are still unidentified) in patients diagnosed late are associated with pancreatic sufficiency and also with mild pulmonary disease. It is doubtful that pancreatic and pulmonary status are determined entirely by independent genetic factors.[28]

The authors thank Drs Scheffer and Van der Hout (Department of Medical Genetics, University of Groningen) and Drs Halley and Van den Ouweland (Department of Clinical Genetics, University Hospital Rotterdam) for performing the DNA analysis.

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